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| (54) Title: DIMERIC COMPOUNDS AND AS INHIBITORS OF NEURAMINIDASE (57) Abstract <p>This invention relates to novel dimeric compounds, methods for their preparation, pharmaceutical formulations thereof, and their use as antiviral agents. The compounds are particularly useful against influenza virus. In particular the invention provides a dimeric compound which comprises two neuraminidase binding molecules attached to a spacer or linking group. Preferably the dimeric molecule comprises two neuraminidase-binding neuraminic acid (sialic acid) or cyclopentyl or cyclohexenyl carboxylic acid derivatives covalently attached to a common spacer group. Pharmaceutical compositions and methods of treatment, prophylaxis and diagnosis are disclosed and claimed.</p> | | |

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DIMERIC COMPOUNDS AND AS INHIBITORS OF NEURAMINIDASE

This invention relates to a new class of chemical compounds and their use in medicine. In particular the invention concerns novel dimeric compounds, methods for their preparation, pharmaceutical formulations thereof and their use as antiviral agents.

BACKGROUND OF THE INVENTION

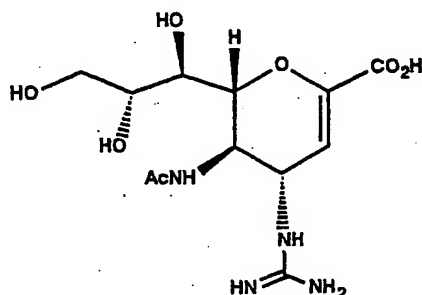
Enzymes with the ability to cleave N-acetyl neuraminic acid (NANA), also known as sialic acid, from other carbohydrates are present in many microorganisms. These include bacteria such as *Vibrio cholerae*, *Clostridium perfringens*, *Streptococcus pneumoniae* and *Arthrobacter sialophilus*, and viruses such as influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus and Sendai virus. Most of these viruses are of the orthomyxovirus or paramyxovirus groups, and carry a neuraminidase activity on the surface of the virus particles. Many of these neuraminidase-possessing organisms are major pathogens of man and/or animals, and some, such as influenza virus and Newcastle disease virus, cause diseases of enormous importance.

It has long been thought that inhibitors of neuraminidase might prevent infection by neuraminidase-bearing viruses. Most of the known neuraminidase inhibitors are analogues of neuraminic acid, such as 2-deoxy-2,3-dehydro-N-acetylneuraminic acid (DANA) and some of its derivatives (Meindl et al, Virology, 1974 58 457). Our International Patent Publication No. WO 91/16320 describes a number of analogues of DANA which are active against viral neuraminidase, and it has been shown in particular that 4-guanidino-2-deoxy-2,3-dehydro-N-acetylneuraminic acid (Compound (A), code number GG167) is useful in the treatment of influenza A and B (N. Engl. J. Med., 1997 337 874-880). Other patent applications describe various closely-related sialic acid derivatives

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(eg. PCT Publications No. WO 95/18800, No. WO 95/20583 and No. WO 98/06712), and anti-viral macromolecular conjugates of GG167 have also been described (International Patent Application No. PCT/AU97/00771).

5



Compound (A)

Ac represents acetyl

10

In addition to the sialic acid based inhibitors mentioned above, other types of highly active inhibitors of influenza virus neuraminidase have also been described, particularly those based on 5- and 6-membered carbocyclic ring systems (eg. International Patent Publications No. WO 96/26933 and No. 97/47194).

Recently, International Patent Publication No. WO 97/06157, No. WO 98/06712 and European Patent Application No. 0823428 have described certain derivatives of compound (A) in which the normal sialic acid 7-hydroxy group is replaced by various other functionalities, which inhibit multiplication of the influenza virus.

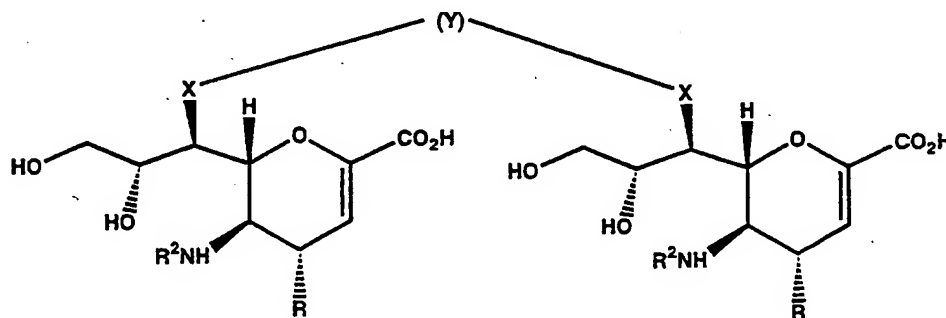
We have now surprisingly found that when two neuraminidase-binding compounds are suitably linked together through a region of the molecule that is not involved in binding to the active site, the resultant dimers show outstanding anti-viral activity. In particular we have found that, although an extra substituent attached to compound (A) at the 7-position generally causes a slight decrease in the anti-influenza activity, when two such 7-substituted molecules of compound (A) are both attached

to a suitable spacer moiety, the anti-influenza activity can be greatly improved. Though not wishing to be bound or limited by any proposed mechanism for the observed effect, we believe that the dimeric compounds of the invention have improved anti-influenza activity because they are able to bind to two separate neuraminidase molecules, and thereby cause aggregation of the neuraminidase tetramers and/or the influenza virions.

10 SUMMARY OF THE INVENTION

In a first aspect the invention provides a dimeric compound which comprises two neuraminidase binding molecules attached to a spacer or linking group. The neuraminidase binding molecule may be any compound which binds to the active site of influenza virus neuraminidase, provided that it is not cleaved by the enzyme. The neuraminidase binding molecule should itself have a high binding affinity, preferably an IC_{50} of $10^{-6}M$ or better. Preferably the dimeric molecule comprises two neuraminidase-binding neuraminic acid (sialic acid) or cyclopentyl or cyclohexenyl carboxylic acid derivatives covalently attached to a common spacer group.

In a preferred embodiment, the invention provides a compound of General Formula I



(I)

- 4 -

in which the neuraminidase binding group is a 2,3-dehydrosialic acid derivative which is attached to a spacer group Y via the 7-position;

5 R represents an azido group, a hydroxy group, an unsubstituted or substituted guanidino group, or an unsubstituted or substituted amino group;

R² represents COCH₃, COCF₃, SO₂CH₃ or SO₂CF₃;

X represents O, O(C=O), NH, NHCO, O(C=O)NH, O(C=S)NH, NH(C=O)NH, or NH(C=S)NH;

10 and the spacer group Y is an optionally substituted and/or branched chain of up to 100 atoms in length, with the backbone atoms selected from the group consisting of carbon, nitrogen, oxygen and sulphur;

or a pharmaceutically-acceptable derivative or
15 salt thereof.

Preferably the spacer group is 8 to 100, more preferably 10 to 50, even more preferably 12 to 30 atoms long.

Most preferably:

20 R is an amino or guanidino group;

R² is acetyl or trifluoroacetyl;

X is O(C=O)NH; and

Y is a linking group of between 10 and 50 atoms in length.

25 Molecular modelling studies indicate that the spacer group could be as short as 18, 15 or 10 atoms long, or may even be shorter than this. The person skilled in the art will readily be able to optimize the spacer length by routine trial and error experimentation.

30 In general it is intended that when any variable occurs twice in formula (I), the variable may be the same or different.

Where R is an amino or guanidino group, suitable substituents include, but are not limited to,
35 alkyl, hydroxyalkyl, allyl, nitrile, alkoxycarbonyl and acyl.

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Suitable spacer groups Y include, but are not limited to, optionally substituted straight or branched hydrocarbon chains, peptides, oligosaccharides, poly amino acids, polyethylene glycol units, alkylamidoalkanes, 5 alkylureidoalkanes, any of which may be used alone, in multiple forms or in combination. The spacer group Y may also optionally have attached to it an extra functionality to improve the pharmaceutical or pharmacokinetic properties of the compound. Such functionalities include lipophilic 10 hydrocarbon groups, polyethylene glycol (PEG) chains and peptides.

For the purposes of this specification, the terms "hydrocarbon", "alkane" or "alkyl" are intended to include saturated, unsaturated and cyclic hydrocarbon groups, 15 aromatic rings, and combinations of such groups. Suitable substituents on hydrocarbon chains include Br, Cl, F, I, CF₃, NH₂, substituted amino groups such as NHacyl, and alkoxy groups such as methoxy and hydroxy, and are preferably F, Cl, hydroxy, alkoxy, amino, alkylamino or 20 carboxy.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds of formula 25 (I). Of particular interest as such derivatives are compounds modified at the carboxyl function, hydroxyl functions or at amino groups. Thus compounds of interest include alkyl esters, such as methyl, ethyl, propyl or isopropyl esters, aryl esters, such as phenyl, benzoyl 30 esters, and acetyl esters of the compounds of formula (I).

It will be appreciated by those skilled in the art that the pharmaceutically acceptable derivatives of the compounds of formula (I) may be derivatised at more than one position.

35 The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) or any other

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compound which, upon administration to the recipient, is capable of providing a compound of formula (I) or an antivirally active metabolite or residue thereof. Of particular interest as derivatives are compounds modified at the sialic acid carboxy or glycerol hydroxy groups, or at amino and guanidine groups.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (eg. sodium), alkaline earth metal (eg. magnesium), ammonium, and NR_4^+ (where R is C_{1-4} alkyl) salts.

The compounds of formula (I) possesses antiviral activity. In particular these compounds are inhibitors of viral neuraminidase of orthomyxoviruses and paramyxoviruses, for example the viral neuraminidase of influenza A and B, parainfluenza, mumps and Newcastle disease.

Thus in a second aspect the invention provides a compound of the invention, preferably a compound of formula (I) or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic agent in the treatment of orthomyxovirus and paramyxovirus infections.

In a third aspect the invention provides a method for the treatment of a viral infection, for example orthomyxovirus and paramyxovirus infections in a mammal,

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comprising the step of administration of an effective amount of a compound of the invention, preferably a compound of formula (I), or a pharmaceutically acceptable salt or derivative thereof, to a mammal in need of such treatment.

In a preferred embodiment of this aspect of the invention there is provided a method for the treatment of influenza A or B in a mammal, comprising the step of administration of an effective amount of a compound of the invention, preferably a compound of formula (I), or a pharmaceutically acceptable salt or derivative thereof, to a mammal in need of such treatment.

Preferably the mammal is a human.

In a fourth aspect the invention provides use of a compound of the invention for the manufacture of a medicament for the treatment of a viral infection.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis against infection as well as to the treatment of established infections or symptoms.

The compounds of the invention may also be used in diagnostic methods, in particular methods for the detection of influenza virus. For use in such methods it may be advantageous to link a compound of the invention to a label.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, a suitable dose will be in the range of from about 0.01 to 100 mg/kg of bodyweight per day, preferably in the range of 0.05 to 10 mg/kg/day, most preferably in the range of 0.1 to 1 mg/kg/day.

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Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However the compounds are also effective when given post-infection, for example after the appearance of established symptoms.

Suitably treatment is given 1-4 times daily and continued for 3-7 days post-infection, eg. 5 days, depending upon the particular compound used.

The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form, for example containing 1 to 1000 mg, conveniently 2 to 200 mg, most conveniently 50 to 100 mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

Thus in a fifth aspect the invention provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not being deleterious to the recipient thereof.

The compounds of the invention may also be used in combination with other therapeutic agents, for example other anti-infective agents. In particular the compounds of the invention may be employed with other antiviral agents. The invention thus provides in a sixth aspect a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof

together with another therapeutically active agent, in particular an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus such formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

Suitable therapeutic agents for use in such combinations include other anti-infective agents, in particular anti-bacterial and anti-viral agents such as those used to treat respiratory infections. For example, other compounds effective against influenza viruses, such as the sialic acid analogues referred to above, amantadine, rimantadine and ribavirin, may be included in such combinations.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compounds of the invention are used with a second therapeutic agent active against the same virus, the dose of each compound may either be the same as or different from that employed when each compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration, or those in a form suitable for administration to the respiratory tract (including the nasal passages) for example by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units, and may be prepared by any of the methods well known in the art of pharmacy. These methods include the step of bringing into association the active compound with liquid carriers or finely divided

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solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may for example be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles, which may include edible oils, or preservatives.

The compounds according to the invention may also be formulated for parenteral administration by injection, for example bolus injection, or continuous infusion, and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, eg. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

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Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base, and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and gum acacia or gum tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin or sucrose and gum acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For administration to the respiratory tract, including intranasal administration, the neuraminidase inhibitors may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract.

Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example

sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol or polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates (eg. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurised pack with a suitable propellant, such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the compounds may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder

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composition may be presented in unit dose form, for example in capsules or cartridges of eg. gelatin, or blister packs from which the powder may be administered by means of an inhaler.

- 5 In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size, for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example
10 by micronisation.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

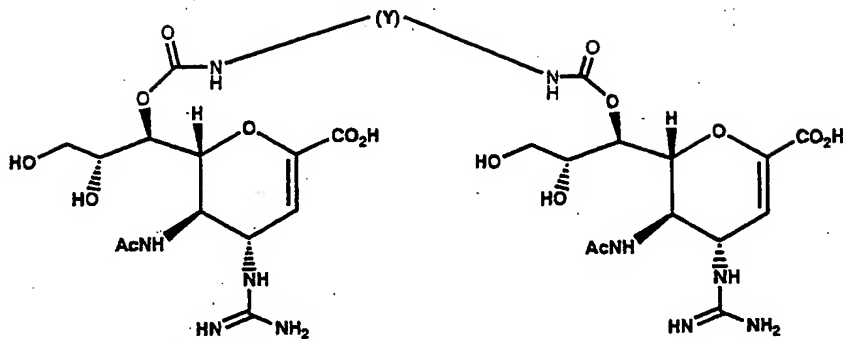
- For the purposes of this specification it will be clearly understood that the word "comprising" means
15 "including but not limited to", and that the word "comprises" has a corresponding meaning.

DETAILED DESCRIPTION OF THE INVENTION

- The invention will now be described in detail by
20 way of reference only to the following non-limiting examples.

Particular examples of compounds of the invention include those of Formula (Ia), in which the spacer group Y is as shown in Table 1 below.

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(Ia)

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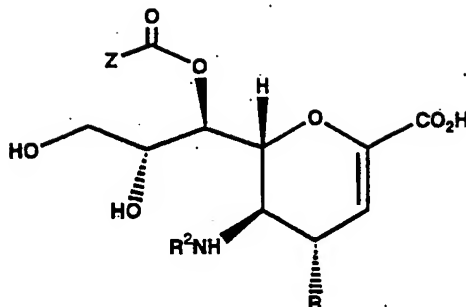
Table 1

| Compound Number | Linking Group Y |
|-----------------|---|
| (2) | $(\text{CH}_2)_6\text{NHCONH}(\text{CH}_2)_4\text{NHCONH}(\text{CH}_2)_6$ |
| (3) | $(\text{CH}_2)_6\text{NHCONH}(\text{CH}_2)_{12}\text{NHCONH}(\text{CH}_2)_6$ |
| (4) | $(\text{CH}_2)_6\text{NH}[\text{COCH}_2\text{NH}]_3\text{CONH}(\text{CH}_2)_6\text{NHCO}[\text{NHCH}_2\text{CO}]_3\text{NH}(\text{CH}_2)_6$ |
| (5) | $(\text{CH}_2)_6\text{NH}[\text{CO}(\text{CH}_2)_5\text{NH}]_2\text{CONH}(\text{CH}_2)_{12}\text{NHCO}[\text{NH}(\text{CH}_2)_5\text{CO}]_2\text{NH}(\text{CH}_2)_6$ |
| (6) | $(\text{CH}_2)_6\text{NH}[\text{CO}(\text{CH}_2)_5\text{NH}]_4\text{CONH}(\text{CH}_2)_6\text{NHCO}[\text{NH}(\text{CH}_2)_5\text{CO}]_4\text{NH}(\text{CH}_2)_6$ |
| (8) | $(\text{CH}_2)_6\text{NHCOCH}_2\text{N}[\text{CH}_2\text{CO}_2\text{H}]\text{CH}_2\text{CH}_2\text{N}[\text{CH}_2\text{CO}_2\text{H}]\text{CH}_2\text{CONH}(\text{CH}_2)_6$ |
| (9) | $(\text{CH}_2)_6\text{NHCO}(\text{CH}_2)_2\text{CH}[\text{NH}_2, \text{TFA}]\text{CONHCH}_2\text{CONH}(\text{CH}_2)_6$ |
| (10) | $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ |

10 The compounds of the invention may be prepared by the methods outlined below, in which R and R² are as defined for formula (I).

Suitable monomeric intermediate compounds of general formula (II) can be prepared following methods described in International Patent Publications
 15 No. WO 97/06157 and No. WO 97/32214. Thus if the group at position 7 is an arylcarbonate (eg. Z = 4-nitrophenoxy), the intermediate can be used to make 7-carbamate derivatives (Z = alkyl-NH) by reaction with various amines (alkyl-NH₂).

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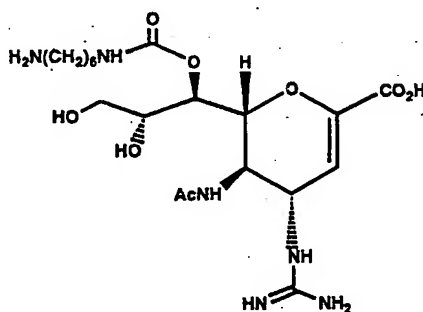


(II)

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For example, the (6-aminoethyl)-7-carbamate derivative of GG167, compound (7) below, is a useful precursor to certain compounds of the invention. As will be appreciated by those skilled in the art, it may be necessary or desirable to use protecting groups to protect one or more of the functional groups of the neuraminidase-binding molecule during the process of attaching the monomers to the spacer group. See for example "Protective Groups in Organic Synthesis" by Theodore W. Greene and P.G.M. Wuts (John Wiley & Sons, 1991).

15



Compound (7)

20

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Example 1 Preparation of Bis-[7-(6'-ethylene-ureidohexyl)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradecoxy-D-glycero-D-galacto-non-2-enopyranosonic acid] (2)

5 To a solution of 5-acetamido-7-(6'-aminohexyl)-carbamoyloxy-4-guanidino-2,3,4,5-tetradecoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (7) (50 mg, 0.1055 mmole) in a mixture of DMSO (1 ml) and pyridine (2.5 ml) were added 1,4-diisocyanatobutane (7.39 mg, 0.0527 mmole) and
10 4-dimethylaminopyridine (12.87 mg, 0.1055 mmole). The whole mixture was stirred under argon at 50°C for 7 days. The mixture was filtered and the filtrate was evaporated under high vacuum to dryness. The residue was stirred in
15 acetone (2 x 20 ml) at room temperature for 24 hr and filtered. The filter-cake was washed with acetone (5 ml) and recrystallized from a mixture of methanol and water (7:3) to afford the title compound (2) as a white solid (18.6 mg, 32%).

20 MS 1090 (M+2)⁺⁺

¹H-nmr (CD₃OD + D₂O) δ (ppm): 1.30-1.70 (m, 20H), 2.01 (br s, 6H), 2.95-3.20 (m, 12H), 3.50-3.65 (m, 2H), 3.70-3.80 (m, 2H), 3.90-4.20 (m, 4H), 4.35-4.70 (m, 6H), 5.70 (br, 2H).
25

Example 2 Preparation of Bis-[7-(6'-hexyleneureido)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradecoxy-D-glycero-D-galacto-non-2-enopyranosonic acid] (3)

30 To a solution of 5-acetamido-7-(6'-aminohexyl)-carbamoyloxy-4-guanidino-2,3,4,5-tetradecoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (7) (50 mg, 0.1055 mmole) in a mixture of DMSO (1 ml) and pyridine (2.5 ml) were
35 added 4-dimethylaminopyridine (12.87 mg, 0.1055 mmole) and 1,12-diisocyanatododecane (13.31 mg, 0.0527 mmole). The whole mixture was stirred under argon at 50°C for 7 days

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and then filtered. The filtrate was evaporated under high vacuum to dryness. The residue was taken up in acetone (2 x 30 ml), redissolved in DMSO (1 ml), then diluted with a mixture of acetone and ether (1:1) (100 ml) to afford a white precipitate. After filtration, the filter cake was washed with acetone (20 ml) and air-dried to give a crude product (3), which was then recrystallized from a mixture of methanol and water to afford the title compound (3) as a white powder (15 mg, 23.6%).

10

MS 1202 (M+2)⁺⁺

¹H-nmr (CD₃OD + D₂O) δ (ppm): 1.25-1.70 (m, 36H), 1.98 (br, s, 6H), 2.95-3.20 (m, 12H), 3.35-3.70 (m, 4H), 3.80-4.60 (m, 10H), 5.65 (br, 2H).

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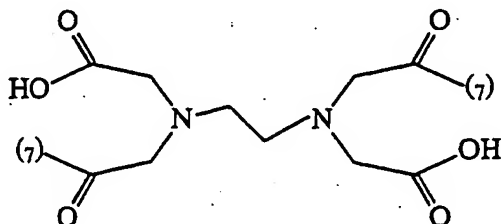
Example 3 Preparation of amino acid linked Bis-[GG167-7-carbamate]; Compounds No. (4), (5) and (6)

In a similar manner to that described in Examples 1 and 2, compounds (4), (5) and (6) were each prepared using the 6-aminohexyl-7-carbamate compound (7), or protected forms of (7), as the key starting material. Each compound was characterised by its mass spectrum and Nmr data.

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Example 4 Preparation of Bis-[7-(6'-methyleneamine-N-acetic acid-N-acetamido-hexyl)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid] (Compound Number (8))

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To a solution of 5-acetamido-7-(6'-aminohexyl)-
 carbamoyloxy-4-guanidino-2,3,4,5-tetradexoxy-D-glycero-D-
 galacto-non-2-enopyranosonic acid (7) (76 mg, 0.16mmole) in
 5 a mixture of DMF (7.5 ml) and pyridine (2.5 ml) were added
 ethylenediaminetetraacetic dianhydride (20.5 mg, 0.08mmole)
 and 4-(dimethylamino)pyridine (3.5 mg, 0.028mmole). The
 whole mixture was stirred at 50°C for 18 hr, then
 evaporated to dryness under high vacuum. The residue was
 10 partitioned between dichloromethane (20 ml) and water (10
 ml). The aqueous solution was washed with dichloromethane
 (10 ml); ethyl acetate (10 ml), then evaporated to dryness
 under high vacuum. The residue was triturated in acetone
 (50 ml x 2) and filtered. The solid was dissolved in water
 15 (0.5 ml) and chromatographed on a Sephadex G-25 (50 ml)
 column using water as eluent and the product was freeze-
 dried, to afford the title compound (8) (30 mg, 31%).

MS 1206 (M+2)

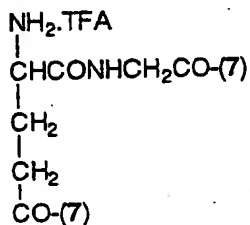
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¹H-nmr (D₂O) δ (ppm): 1.23-1.63 (m, 16H), 1.98 (brs, 6H),
 3.00-3.20 (m, 8H), 3.35-3.55 (m, 6H), 3.60-3.92 (m, 10H),
 4.08 (m, 4H), 4.43 (dd, 2H), 4.50 (dd, 2H), 4.84 (dd, 2H),
 5.66 (br, 2H).

25

Example 5 Preparation of D-glutam-γ-yl-α-ylamineacetyl,
di-[7-(6'-aminohexyl)-carbamoyloxy-5-
acetamido-4-guanidino-2,3,4,5-tetradexoxy-D-
glycero-D-galacto-non-2-enopyranosonic acid]
 30 as trifluoroacetic acid salt (Compound
Number (9))

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N-Boc-D-glutam- α -ylamineacetic acid (25 mg, 0.082mmole) was dissolved in water (0.25 ml) containing triethylamine (16.6 mg, 0.164mmole) and N-methylmorpholine (16.6 mg, 0.164mmole). The clear solution was diluted with acetone (3 ml), then cooled to -20°C in a dry ice-acetone bath. Into this solution was added isobutyl chloroformate (26.95 mg, 0.197mmole). The reaction mixture was stirred at $-15^{\circ}\pm 2^{\circ}\text{C}$ for 12 min., then combined with a solution of 5-acetamido-7-(6'-aminohexyl)carbamoyloxy-4-guanidino-2,3,4,5-tetradecoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (7) (116.9 mg, 0.246mmole) and triethylamine (24.9 mg, 0.246 mmole) in water (2.5 ml). The resulting mixture was allowed to agitate at room temperature for 3 hr, then evaporated to dryness under reduced pressure. The residue was subjected to flash column-chromatography (silica gel, 2-propanol:acetic acid:water = 3:1:1 as eluent) to afford the N-Boc derivative of the title compound (9), which was then treated with trifluoroacetic acid (2 ml) at room temperature for 1 hr, evaporated under vacuum to dryness. The residue was freeze-dried to give the title compound (9) as trifluoroacetic acid salt (31 mg, 30.4 %).

MS 1118 (M+2)

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^1H -nmr (D_2O) δ (ppm): 1.22-1.62 (m, 16H), 1.98 (br., 6H), 2.20 (m, 2H), 2.41 (m, 1H), 2.57 (m, 1H), 2.90-3.25 (m, 8H), 3.59 (br dd, 2H), 3.68 (br dd, 2H), 3.76-4.01 (m, 3H), 4.10 (m, 4H), 4.43 (br dd, 2H), 4.53 (br dd, 2H), 4.95 (br dd, 2H), 5.85 (br., 2H)

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Example 6 Inhibition of Influenza Virus Replication by Compounds of the Invention

Compounds of the invention were tested for their ability to inhibit the replication of influenza A virus, following the standard method that has been described in the literature (see for example Watanabe et al, J.

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- 20 -

Virological Methods, 1994 48 257). The assay was carried out using MDCK cells, and the results are shown in Table 2 below. The results are shown as ID₅₀, the minimum compound concentration that inhibits cytopathic effect by 50%

5 [(µg/ml)], calculated by using a regression analysis program for semi-log curve fitting. The results show that dimeric compounds (2), (3) and (4) are all more active against influenza than the monomeric ligand molecule (7), and that compound (2) of the invention is even more potent
10 than the highly active compound (A) [GG167]. The therapeutic index for the compounds can be calculated by dividing the minimum cytotoxic drug concentration (MTC) by the ID₅₀.

15

Table 2

| Compound No. | Spacer Atoms | ID ₅₀ | ID ₅₀ | MTC |
|--------------|-------------------|------------------|------------------|-------|
| | (Number of atoms) | µg/ml | (µM of (A)) | µg/ml |
| (2) | 22 | 0.007 | 0.013 | >10 |
| (3) | 30 | 0.017 | 0.028 | >10 |
| (4) | 42 | 0.084 | 0.11 | >10 |
| (5) | 58 | 0.35 | 0.42 | >10 |
| (6) | 78 | 0.63 | 0.62 | >10 |
| (A) | ----- | 0.0095 | 0.028 | >10 |
| (7) | ----- | 0.22 | 0.32 | >10 |

Example 7 Inhibition of Influenza Virus Replication by
compounds of the invention

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Compounds of the invention were tested for their ability to inhibit the replication of influenza A/Victoria/3/75 B010 in a standard CPE type assay similar to that described above in Example 6. The results for

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three separate experiments are shown in Table 3 below.

Table 3

| Compound No. | EC ₅₀ (µg/ml) | EC ₉₀ (µg/ml) | CC ₅₀ (µg/ml) |
|-----------------------|--------------------------|--------------------------|--------------------------|
| 8 (test 1) | 0.00971 | 0.0671 | > 0.1 |
| 9 (test 2) | 0.002 | - | > 1 |
| 9 (test 3) | 0.0004 | - | > 0.1 |
| Compound (A) (test 2) | 0.009 | - | > 1 |
| Compound (A) (test 3) | 0.009 | - | > 0.1 |

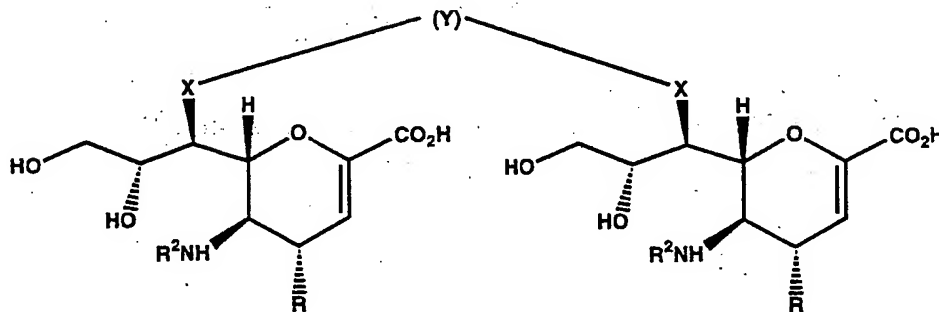
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It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

10

CLAIMS

1. A dimeric compound which comprises two neuraminidase binding molecules attached to a spacer or linking group, or a pharmaceutically acceptable salt or derivative thereof, in which the neuraminidase binding molecule is a compound which binds to the active site of influenza virus neuraminidase, but is not cleaved by the enzyme.
2. A compound according to Claim 1, in which the neuraminidase binding molecule has an IC_{50} of not more than $10^{-6}M$.
3. A compound according to Claim 1 or Claim 2, in which the dimeric molecule comprises two neuraminidase-binding neuraminic acid (sialic acid) or cyclopentyl or cyclohexenyl carboxylic acid derivatives covalently attached to a common spacer group.
4. A compound according to any one of Claims 1 to 3, in which the compound is of General Formula I



(I)

- in which the neuraminidase binding group is a 2,3-dehydrosialic acid derivative which is attached to a spacer group Y via the 7-position;

R represents an azido group, a hydroxy group, an unsubstituted or substituted guanidino group, or an unsubstituted or substituted amino group;

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R^2 represents COCH_3 , COCF_3 , SO_2CH_3 or SO_2CF_3 ;
X represents O, $\text{O}(\text{C}=\text{O})$, NH, NHCO , $\text{O}(\text{C}=\text{O})\text{NH}$, $\text{O}(\text{C}=\text{S})\text{NH}$,
 $\text{NH}(\text{C}=\text{O})\text{NH}$, or $\text{NH}(\text{C}=\text{S})\text{NH}$;

and the spacer group Y is an optionally
5 substituted and/or branched chain of up to 100 atoms in
length, with the backbone atoms selected from the group
consisting of carbon, nitrogen, oxygen and sulphur;

or a pharmaceutically-acceptable derivative or
salt thereof.

10 5. A compound according to any one of Claims 1 to 4,
in which the spacer group is 8 to 100 atoms long.

6. A compound according to Claim 5, in which the
spacer group is 10 to 50 atoms long.

7. A compound according to Claim 6, in which the
15 spacer group is 12 to 30 atoms long.

8. A compound according to any one of Claims 1 to 4, in
which:

R is an amino or guanidino group, which may
optionally be substituted;

20 R^2 is acetyl or trifluoroacetyl;

X is $\text{O}(\text{C}=\text{O})\text{NH}$; and

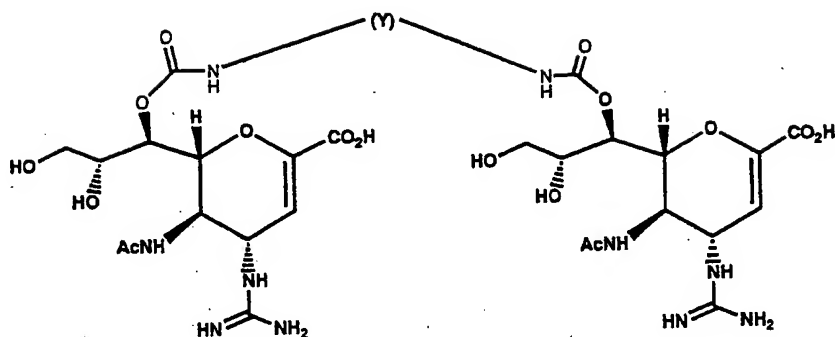
Y is a linking group of between 10 and 50 atoms
in length.

9. A compound according to Claim 8, in which the
25 substituent on the R group is selected from the group
consisting of alkyl, hydroxyalkyl, allyl, nitrile,
alkoxycarbonyl and acyl.

10. A compound according to any one of Claims 1 to
9, in which the spacer group Y is selected from the group
30 consisting of optionally substituted straight or branched
hydrocarbon chains, peptides, oligosaccharides, poly amino
acids, polyethylene glycol units, alkylamidoalkanes,
alkylureidoalkanes, any of which may be used alone, in
multiple forms or in combination.

35 11. A compound according to any one of Claims 1 to
10, in which the compound is of formula (Ia)

- 24 -



(Ia)

- 5 and Y is one of the linking groups set out in Table 1 herein.
12. A compound according to any one of Claims 1 to 11, in which the spacer group Y has attached to it an extra functionality to improve the pharmaceutical or
- 10 pharmacokinetic properties of the compound, selected from the group consisting of lipophilic hydrocarbon groups, polyethylene glycol (PEG) chains and peptides.
13. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 12, together
- 15 with a pharmaceutically acceptable carrier and, optionally, one or more other therapeutic and/or prophylactic ingredients.
14. A composition according to claim 13, additionally comprising a second anti-viral agent.
- 20 15. A composition according to claim 13, in which the second anti-viral agent is selected from the group consisting of sialic acid analogues, amantadine, rimantadine and ribavirin.
16. A method for the treatment or prophylaxis of an
- 25 orthomyxovirus or paramyxovirus infection in a mammal, comprising the step of administration of an effective amount of a compound according to any one of Claims 1 to 12 to a mammal in need of such treatment.
17. A method according to Claim 16, in which the
- 30 infection is caused by influenza A or B.

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18. A method according to Claim 16 or claim 17, in which the mammal is a human.
19. A method according to any one of Claims 16 to 18, in which the compound is of Formula (I) or Formula (Ia).
- 5 20. A method according to any one of Claims 16 to 19, in which the dose is in the range of from about 0.01 to 100 mg/kg of bodyweight per day.
21. A compound according to any one of Claims 1 to 12, for use as an active therapeutic agent in the treatment or prophylaxis of orthomyxovirus or paramyxovirus
10 infections.
22. Use of a compound according to any one of Claims 1 to 12 for the manufacture of a medicament for the treatment or prophylaxis of a viral infection.
- 15 23. A method for the detection of influenza virus, comprising the step of contacting a compound according to any one of Claims 1 to 12 with a sample suspected of comprising the virus.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00165

| A. CLASSIFICATION OF SUBJECT MATTER | | | | |
|--|---|--|---|---|
| Int. Cl. ⁷ : C07D 309/28, A61K 31/7012, 31/351, A61P 31/16 | | | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | | | |
| B. FIELDS SEARCHED | | | | |
| Minimum documentation searched (classification system followed by classification symbols) | | | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | | | |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN Substructure Search MEDLINE, CA, WPIDS, BIOSIS: dimer?, link?, spacer, bis?, neuramini?, sialic acid, sialidase, bind | | | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | | |
| X | US 5759823 (WONG, CHI-HUEY et al) 2 June 1998 Column 4 formula (II), column 12 formulae (IV) and (V), Table 1 compound 1y and (GlcNAc) _n | 1-3, 13 | | |
| X | Derwent Abstract Accession No: 98-12068/11, B04 D16 JP-193279, & WO 98/03524 see abstract, (SEIKAGAKU) 29 January 1998 Compounds (I) and (III) | 1-3, 13 | | |
| X | WO 97/33896 (GELTEX PHARMACEUTICALS, INC.) 18 September 1997 Claims 1, 13 | 1-15 | | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex | | | | |
| <p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </td> </tr> </table> | | | <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> | <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> |
| <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> | <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> | | | |
| Date of the actual completion of the international search 5 April 2000 | | Date of mailing of the international search report 20 APR 2000 | | |
| Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929 | | Authorized officer CHRISTINE BREMERS Telephone No : (02) 6283 2313 | | |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU00/00165

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|-----------------------|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | WO 97/31006 (GLYCOMED INCORPORATED) 28 August 1997 See whole document especially claims 1-7 | 1-15 |
| X | WO 96/26933 (GILEAD SCIENCES, INC.) 6 September 1996 Page 2 line 23 - page 8 line 25, page 15 lines 14 and 22; claims 1, 4, 58, 65, 113-115 Compounds (I), (II), (VII), (VIII) | 1-3, 13 |
| X | US 5243035 (NAKABAYASHI, S et al) 7 September 1993 Column 2 line 25 - column 3 line 65, column 11 compounds (xxxii), (xxxiv), (xxxv), Claim 1 | 1-3, 13 |
| X | WO 93/17033 (THE BIOMEMBRANE INSTITUTE) 2 September 1993 Claims 1-3 | 1-15 |
| X | Virology, Vol 58 No: 2 (1974) pages 457-463 (MEINDL, P et al) "Inhibition Of Neuraminidase Activity by Derivatives of 2-Deoxy-2,3-dehydro-N-acetyl- Neuraminic Acid" Page 459 column 1 line 15 - column 2 line 19, compound 12 | 1-3, 13-23 |
| X | Monatshefte für Chemie Vol 104 No: 2 (1973) pages 402-414 (MEINDL, P et al) "Synthese und Eigenschaften von 2-Deoxy-2,3-dehydroneuraminsäure sowie neuer N- Acylderivative" compound 19 page 406 | 1-3 |
| A | WO 94/06467 (BRIGHAM AND WOMEN'S HOSPITAL, INC.) 31 March 1994 Claims 1, 25 and 26 | 1-3, 13 |
| A | EP 747063 (CONNAUGHT LABORATORIES LIMITED) 11 December 1996 Page 3 line 20 - page 4 line 24, claim 1 | 1-15 |

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/00165

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent Document Cited in Search Report | | Patent Family Member | | | | | |
|--|---------|----------------------|----------|----|----------|----|----------|
| US | 5759823 | AU | 16680/92 | CA | 2106301 | EP | 576592 |
| | | JP | 6505638 | US | 5278299 | WO | 9216640 |
| | | US | 5461143 | US | 5593887 | AU | 21459/92 |
| | | WO | 9221657 | US | 5276120 | US | 5596005 |
| | | US | 5403726 | AT | 174925 | AU | 27854/92 |
| | | BG | 98713 | CZ | 9400842 | DE | 69228005 |
| | | EP | 642526 | ES | 2129458 | FI | 941732 |
| | | HU | 9401072 | JP | 7500248 | NO | 941346 |
| | | SK | 425/94 | WO | 9308205 | AU | 672029 |
| | | CA | 2139506 | EP | 654087 | IL | 106366 |
| JP | 193279 | JP | 8500012 | NZ | 255109 | WO | 9402624 |
| | | JP | 58094013 | | | | |
| | | AU | 20787/97 | CA | 2250319 | EP | 888368 |
| | | US | 5891862 | | | | |
| | | AU | 21372/97 | EP | 882057 | US | 5837689 |
| | | US | 5750508 | US | 5658880 | US | 5789385 |
| | | AU | 33259/95 | CA | 2197336 | EP | 775151 |
| | | JP | 10507742 | WO | 9605209 | AU | 58552/96 |
| | | CA | 2221589 | EP | 828729 | JP | 11507020 |
| | | WO | 9636627 | AU | 21365/97 | EP | 882034 |
| WO | 9626933 | WO | 973094 | | | | |
| | | AU | 53571/96 | BR | 9607098 | CA | 2188835 |
| | | CN | 1147813 | CZ | 9702690 | EP | 759917 |
| | | EP | 976734 | ES | 2118674 | HU | 9800026 |
| | | JP | 11501908 | NO | 973908 | PL | 32200 |
| | | SI | 9620042 | US | 5866601 | US | 5952375 |
| | | CA | 2050484 | EP | 489162 | WO | 9113079 |
| | | JP | 2563712 | | | | |
| | | EP | 521692 | EP | 638085 | JP | 6145190 |
| | | JP | 7504222 | AU | 86677/91 | CA | 2089375 |
| US | 5243035 | EP | 546122 | JP | 6501008 | WO | 9204048 |

| | | | | | | | |
|----|---------|----|---------|----|---------|----|---------|
| WO | 9406467 | AU | 690525 | EP | 667787 | FI | 951412 |
| | | IL | 107103 | JP | 8501563 | NO | 951109 |
| | | NO | 951152 | NZ | 248766 | ZA | 9307034 |
| | | US | 5843461 | US | 5795580 | US | 5993825 |
| EP | 747063 | CA | 2178517 | US | 5780606 | | |

END OF ANNEX

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